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PHARMACOGENETICS OF ANTIPSYCHOATICS

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ABSTRACT

Although a number of antipsychotics have been introduced for the treatment of schizophrenia, inter-individual differences of in antipsychotic response and the number of refractory schizophrenic patients have become two of the most challenging problems in clinical psychiatry. Thus, the pharmacogenetics of antipsychotics have been aimed at providing genetic components of this inter-individual variability in antipsychotic response in order to establish an individually-based pharmacotherapy for schizophrenia and to elucidate the mechanism of antipsychotic response so as to solve the refractoriness of schizophrenia. Pharmacogenetics, which is defined as the science of pharmacological response and its modification by hereditary influence can be divided into two categories: the genetic background of pharmacokinetics, i.e. the absorption, distribution, tissue localization, biotransformation and excretion of drugs, and pharmacodynamics, i.e. the biochemical and physiological consequences of a drug and its mechanism of action. Pharmacokinetics of antipsychotics has been focused mainly on the association between genetic polymorphisms in CYP genes, including CYP2D6, and the metabolism of these drugs. Polymorphism in CYP2D6 enables a division of individuals within a given population into at least two groups, i.e. poor metabolizers (PMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs) of certain drugs. PMs have higher plasma concentrations of and more adverse effects from antipsychotics. UMs could be one of the important factors that induce treatment-refractoriness to antipsychotics. Genetic polymorphisms in serotonin and dopamine receptors that have a high affinity for antipsychotics have so far been extensively investigated in the pharmacodynamics of this type of drug. Not just one gene but multiple genes play a role in complex phenotypes, including the clinical response to medication. Thus, a multiple candidate genes approach has recently been adopted in the pharmacogenetics of antipsychotics. The new field of pharmacogenomics using DNA microarray analysis, which focuses on the genetic determinants of drug response at the level of the entire human genome, is important for development and prescription of safer and more effective individually-tailored antipsychotics.

Key Words: Antipsychotic, Genetics, Serotonin, Dopamine, Treatment response

INTRODUCTION

Since chlorpromazine was first introduced into clinical psychiatry, various kinds of antipsychotics have been developed and used for schizophrenia. Clinicians, however, still have considerable difficulty in choosing an appropriate antipsychotic for certain patients due to the inter-individual diversities of drug response. No definitive factor that can predict drug-response has yet been identified, although many researchers have tried to discover factors that can predict drug-response, e.g. demographics, and clinical features.

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Moreover, more than 40% of schizophrenic patients demonstrate varying levels of positive symptoms resistant to medication, even though a number of additional antipsychotics have been introduced. If treatment-failure is also defined to include remission of negative, cognitive, and mood symptoms in schizophrenia, the rate of poor response beomes considerably higher. On the other hand, it is essential to identify the mechanism of action of current antipsychotics in order to discover more effective drugs for refractory patients. However, the actual pharmacological mechanism underlying the clinical effects of antipsychotics have yet to be elucidated, although many hypotheses have been proposed.

Some treatment-resistant patients some of them cannot or will not take antipsychotics because of their side effects. Even worse, antipsychotics could cause fatal adverse effects such as malignant syndrome or agranulocytosis, or irreversible side effects such as tardive dyskinesia. Susceptibility to drug-induced side effects also shows inter-individual differences. Thus, indicators that can predict not only therapeutic efficacy but also adverse effects are urgently required in clinical psychiatry.

The importance of genetic factors among inter-individual diversities of drug response has been steadily clarified since the 1950s. As a result, such clarification has given rise to the new field of “pharmacogenetics”, which is defined as the science of pharmacological response and its modification by hereditary influence. The consideration of drug-effects can be divided into two categories: pharmacokinetics and pharmacodynamics, both of which are subject to genetic influence. Although pharmacokinetic studies include the consideration of the absorption, distribution, tissue localization, biotransformation and excretion of drugs, the studies have so far focused mainly on the enzymes of metabolic clearance. Pharmacodynamics is the study of the biochemical and physiological consequences of a drug and its mechanism of action. In most phamacodynamics, the structures of receptors, ion-channels or carrier proteins have been investigated.

The genetic control of a drug-metabolizing enzyme ordinarily occurs via a single locus, whereas because of the complexity of receptor structures, often involving multiple units and proteins, phamacodynamics requires multiple genes and polymorphisms. The complexity of pharmacodynamics gave rise to the new field of pharmacogenomics, which focuses on the genetic determinants of drug response at the level of the entire human genome. Pharmacogenomics can be advanced by the progress of the Human Genome Project and by high-throughput genotyping that enables the creation of high-density single-nucleotide polymorphism (SNP) map.

In this article, the author will review the pharmacokinetics, pharmacodynamics, and pharmacogenomics of antipsychotics.

1. Pharmacokinetics of antipsychotics

Most antipsychotics are extensively metabolized by cytochrome (CYP) P450s that are members of a super-family of oxidative enzymes and that constitute a major system for the oxidative metabolism of therapeutic substances. Thus, the pharmacokinetics of antipsychotics has been focused mainly on the association between genetic polymorphisms in CYP genes and the metabolism of antipsychotic drugs. The CYP2D6 has been most extensively investigated in the field of psychiatry, since this enzyme is involved in the metabolism of many antipsychotics and has many genetic polymorphisms that influence the function of the enzyme. There are more than 70 variant alleles at the CYP2D6 gene locus, including the two most common variants, CYP2D6*4 and CYP2D6*45, encoding non-functional products.[1] Other variants that reduce activity, alter substrate specificity or increase activity have also been described. Compared with

efficient metabolizers (EM), poor metabolizers (PM) show no or reduced CYP2D6 activity by polymorphisms resulting in potentially increased concentrations of metabolized drugs. On the other hand, ultrarapid metabolizers (UM) that can be found in 1% of Caucasians often do not reach therapeutic concentrations and require an increased dose. Pronounced ethnic differences in the prevalence of both PM and UM have been reported; e.g., the frequency of PM is 5 to 10% among Caucasians, about 2% in Asians, and 7–8% in Africans.[2]

PMs have higher plasma concentrations of and suffer more adverse effects from antipsychotics. The incidence of the acute side effects of these drugs, including postural hypotension, excess sedation, or extrapyramidal symptoms, is disproportionately in PMs.[3] On the other hand, it is not clear whether the development of chronic side effects such as tardive dyskinesia is associated with a reduced metabolizing capacity of CYP2D6.

UMs have been reported at increased rates in select groups such as depressive inpatients, possibly due to the high percentage of insufficiently treated cases. Thus, UM can be one of the important factors that induce treatment-refractoriness in the field of psychiatry.

2. Pharmacodynamics of antipsychotics

All receptor and transporter genes for neurotransmitters as well as genes located down-stream of the intracellular signaling pathways can be considered candidate genes for the pharmacodynamics of antipsychotics. It is difficult to select a good candidate gene, since the true mechanism of therapeutic action of antipsychotics has not been clarified yet. However, association studies between genetic polymorphisms in neurotransmitter system and clinical drug-response have been carried out in order to investigate the potential involvement of a specific candidate gene in clinical response. These studies have adopted a candidate gene approach that uses a priori knowledge of drug profiles to identify genes relevant to drug-response. Furthermore, appropriate polymorphisms that influence the function of the gene-product or are merely markers have to be identified for potential candidate genes. So far, genetic polymorphisms in serotonin (5-HT) and dopamine (DA) systems have been extensively investigated in the pharmacodynamics of antipsychotics.

In addition to the selection of appropriate polymorphisms, it is also important to evaluate the clinical response in psychiatric pharmacodynamics, since there is still no biological marker to reflect the degree of severity in schizophrenia. Thus, it is essential to use a reliable and validated rating scale to evaluate clinical symptoms. The Positive and Negative Syndrome Scale (PANSS) or the Brief Psychotic Rating Scale (BPRS) for antispychotics have been used for clinical ratings in pharmacogenetic studies, although some studies have lacked any exact evaluation of clinical responses or definite protocols.

Clozapine is the only antipsychotic which has proven to be effective for treatment-resistant schizophrenia, although it may also induce the fatal adverse effect of agranulocytosis. In addition, the variety of clozapine responses is considerable, ranging from near total remission to little or no response. At present, no reliable means exist to predict who will experience a favorable clozapine response, and no pharmacological mechanism is yet known to explain the efficacy of clozapine for refractory schizophrenia. Thus, pharmacogenetic studies that address antipsychotic-response have focused primarily on clozapine and its variants in candidate genes of DA and 5-HT systems.

1) DA system (Table 1)

The first candidate gene examined with regard to clozapine response was the DA4 receptor

Table 1 Dopaminergic pharmacodynamic studies of antipsychotics

Variant	Influence on function	Findings of pharmacogenetics		Number of reports
		Medication	Result	
DRD4:				
48 bp VNTR	Clozapine-binding	clozapine	n.s.	5
		typical antipsychotics	n.s.	1
		typical antipsychotics	association	2
Val194Gly	Clozapine-binding	clozapine	n.s.	1
DRD3:				
Ser9Gly	Dopamine-binding	clozapine	n.s.	1
		clozapine	association	1
DRD2:				
Ser311Cys	cAMP synthesis	clozapine, typical antipsychotics	n.s.	2
-141Ins/Del	mRNA expression	clozapine	n.s.	3
		bromperidol,nemonapride	association	1
Taq 1 A	Receptor density	Nemonapride, haloperidol	association	2

gene (DRD4), because in addition to its high affinity for clozapine, the DA4 receptor is abundant in the prefrontal cortex, (a brain region thought to be related to the cognitive dysfunction of schizophrenia), and the DRD4 gene itself is highly polymorphic. Among polymorphisms in the DRD4, the 48 bp variable number of tandem repeats (VNTR) has been the most extensively investigated, since the VNTR was shown an in vitro study to influence the sodium chloride sensitivity of clozapine-binding and inhibition of c-AMP synthesis. However, this polymorphism did not seem to have any association with clozapine response.[4] On the other hand, multiple reports have shown an association between a typical antipsychotic response and the VNTR.

The DA3 receptor, which shares homologies with both the DA4 and DA2 receptors, has generated interest, since the DA3 receptor gene (DRDA3) has a known functional polymorphism, Ser9Gly, that influences dopamine binding. However, the association between the Ser9Gly and clozapine response remains controversial.[5]

The DA2 receptor is a major site of the action of conventional antipsychotics such as chlorpromazine and haloperidol, and of some atypical antipsychotics such as risperidone. One functional polymorphism (-141 Ins/Del) in the promoter region, as well as missense variants including Ser311Cer and an intronic variant (Taq 1 A), have been identified in the DA2 receptor gene (DRD2). The -141 Ins/Del polymorphism that influences the expression of the DRD2 was reported to be associated with anxiolytic and antidepressive effects during treatment with two conventional antipsychotics, bromperidol or nemonapride[6], although other studies failed to show any relation between that polymorphism and the clinical response to clozapine as well as other typical antipsychotics. Although theSer311Cer was shown to influence c-AMP synthesis, it has not been associated with clozapine or with a typical antipsychotic response. The Taq 1A that is located in the intron of DRD2 and has been reported to influence the density of the receptor was shown to have an association with the acute effects of a selective DA2 receptor antagonist, nemonapride, and haloperidol.[7]

2) 5-HT system (Table 2)

The 5-HT receptor genes have been regarded as good candidates for pharmacodynamic studies of antipsychotics, since 5-HT mediated mechanisms seem crucial to atypical antipsychotic drug action, including that of clozapine.

Among 14 human 5-HT receptors, the 5-HT2A receptor has received the most attention in

Table 2 Serotonergic pharmacodynamic studies of antipsychotics

Variant	Influence on function	Findings of pharmacogenetics		Number of reports
		Medication	Result	
HTR2A:				
T102C	None	clozapine	n.s.	5
		clozapine	association	3
		risperidone	association	1
-1438A/G	mRNA expression?	clozapine	association	2
Hys452Tyr	Ca ion response	clozapine	n.s.	2
		clozapine	association	2
HT2C:				
Cy23Ser	m-CPP binding	clozapine	n.s.	3
		clozapine	association	1
HTR6:				
C267T	None	clozapine	n.s.	1
		clozapine	association	1

the field of psychophamacogenetics, since it might be involved in the pathophysiogy of hallucination, and since most atypical antipsychotics have a relatively high affinity for the 5-HT2A receptor. An association between the silent polymorphism 102T/C in the 5-HT2A receptor gene (HTR2A) and clozapine has been reported[8], although those findings have not always been replicated.[9] However, a meta-analysis showed that the 102T/C is associated with clozapine response.[10] If this association is accurate, and if we consider that the 102T/C cannot influence the function of the receptor, the other variant that is in linkage disequilibrium with the 102T/C plays a genuine role in clozapine response. The -1438A/G in the promoter region of HTR2A is in linkage disequilibrium with the 102T/C and possibly influences the expression of HTR2A. Furthermore, the -1438A/G was shown to be associated with clozapine response.[11] Another polymorphism in HTR2A, Hys452Tyr[12] was shown to influence the intracellular signal transduction of the 5-HT2A receptor, as measured by Ca^{2+} mobilization induced by 5-HT stimulation. The 452Tyr was associated with both smaller peak amplitude in Ca^{2+} mobilization and a different time course of response, with slower peak latency and a longer half time in the Hys452Tyr heterozygote as compared to the His452His homozygote.[13] The Hys452Tyr was shown to be associated with clozapine response although some studies could not replicate the finding[9].

In addition to the 5-HT2A receptor, other 5-HT receptors, such as 5-HT 2C and 5-HT 6, have also been investigated in psychopharmacognetic studies because atypical antipsychotics also have high affinity for these receptors. The 5-HT2C receptor has been targeted for study based on the high densities of this receptor in brain regions implicated in both the pathophysiology of schizophrenia and the mechanism of action of clozapine as well as other atypical antipsychotics. The Ser23 in the 5-HT2C receptor gene influences m-chlorophenylpiperazine (m-CPP), a nonselective5-HT_{2C} agonist, binding, in comparison with Cys23. Therefore, the Ser23 may be constitutively more active and tends to be more desensitized.[14] The Cys23Ser was reported to have an association with clozapine response, although other studies could not replicate this association.[15] Although silent variant, C267T, in the 5-HT 6 receptor gene was shown to be marginally associated with clozapine response, that association also could not be replicated by any other studies.

3) Future direction: Multiple candidate genes

Not just one gene but multiple genes play a role in complex phenotypes, including the clinical response to medication. Arranz *et al.* published the most comprehensive study to date of a

pharmacogenetics screening strategy: a combination of 6 out of 19 candidate gene variants (in 5-HT2A, 2C, 5-HT transporter and Histamin 2 receptor genes) predicted response to clozapine with a prediction level of 76.9% (95.9 % sensitivity, 38.3 specificity).

We applied this approach combined with haplotype analysis to investigate the pharmacogetics of risperidone, one of the most widely used atypical antipychotics. In our study multiple linear regressions were used to analyze the effects of these haplotypes/genotype of six candidate polymorphisms (HTR2A -1438G>A, 102T>C, H452Y; DRD2 -141delC, *Taq* I A; COMT V158M) on PANSS scale performance of risperidone treatment. Compared with patients who had Ins-A2/Ins-A2 diplotype (n=25), PANSS total scores of patients with Ins-A2/Del-A1 diplotype (n=10) showed 40% greater improved.[16]

3. Pharmacogonenomics

Since individual alleles may contribute only in a small degree to variable drug actions, phamacogenetic studies have not yet reached any definitive conclusion, as mentioned above. An alternative scenario is that it may be possible to identify collections of dozens, hundreds, or even thousands of SNPs that, taken together, might identify a patient as being at high or low risk for either beneficial or toxic drug effects. Thus, phamacogenomic studies encompass the sum of all genes, i.e., the genome, whereas the traditional pharmacogenetic approach relies on studying sequence variations in candidate genes suspected of affecting drug response.

First, progress in the human genome project has given rise to a new approach, i.e., phamacogenomic studies. Second, the high speed and specificity associated with newly emerging genomic technologies such as high-throughput DNA sequencing, gene mapping, and bioinformatics have enabled the search for relevant genes and their variants to include the entire genome.[17]

High-throughput technologies as wal are now being applied to the study of the genomic effects of antipsychotics. Profiling the expression patterns of genes in a target tissue reveals the mechanisms of drug action in a genomic context, and can serve to clarify interindividual differences in drug response that occur some time after the downstream of immediate drug effects in the body. For example, a recent DNA microarray analysis of clozapine-and haloperidol-treated rats identified a multiple differentially altered expression of the genes involved in synaptic function and in the regulation of intracellular Ca2+.[18] Transcript and protein profiling in patients could reveal an antipsychotic fingerprint for responsiveness or nonresponsiveness, as well as a signature motif that may be diagnostic of a specific phenotype. Similarly, antipsychotic-sensitive gene products could provide a new generation of pharmacological targets.

Current concepts in pharmacotherapy basically focuses large patient populations as a whole, in spite of the known inter-individual, genetically-based differences in drug response. In contrast, pharmacogenomics may help focus effective therapy on smaller patient subpopulations characterized by distinct genetic profiles although demonstrating the same disease phenotype. This strategy may also contribute to designing novel, more specific medications and to clarifying the mechanisms of the action of antipsychotics, thus furthering our knowledge of the pathophysiology of schizophrenia.

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